PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference NEU202-11.2	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL03/00240	International filing date *(day/month/year)* 20 March 2003 (20.03.2003)	Priority date *(day/month/year)* 08 April 2002 (08.04.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 9/14 and US Cl.: 424/486		
Applicant NEURIM PHARMACEUTICALS LTD. (1991) LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 September 2003 (26.09.2003)	18 October 2004 (18.10.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer BLESSING FUBARA Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMI[redacted]Y EXAMINATION REPORT

International application No.
PCT/IL03/0024[redacted]

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-20 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 23 and 24, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages 21 and 22, filed with the letter of 05 July 2004 (05.07.2004)

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMI[redacted] EXAMINATION REPORT

International application No.
PCT/IL03/0024[redacted]

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-28	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-28	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-28	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-28 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the composition of claims 15 and the method of claim 1.

In response to applicants' argument, claims 1-14 are treated as method claims.

Mendel teaches a composition that comprises melatonin and trazodone or zaleplon or zolpidem and carrier; the composition is useful in treating sleep disorder including insomnia (column 29, line 13 to column 34 line 33). The amendment of claim 15 removes Mendel as a prior art.

Claims 1-28 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

CLAIMS

1. Use of melatonin in the manufacture of a medicament effective for the short-term potentiation of the hypnotic effect of at least one compound selected from the group consisting of non-barbiturate and non-benzodiazepine hypnotics.

2. Use according to claim 1, which is further characterized by at least one of the following features:

(a) said hypnotics are GABA-A receptor modulators;

(b) said hypnotics are compounds which include a fused-ring system containing ring nitrogen;

(c) said medicament comprises at least one carrier, diluent, coating or adjuvant;

(d) said medicament is in unit dosage form;

(e) said medicament includes at least one compound selected from the group consisting of non-barbiturate and non-benzodiazepine hypnotics;

(f) said at least one compound is present in said medicament and in an amount which, if administered in absence of melatonin, would be a sub-therapeutic amount;

(g) said medicament is adapted for sustained release of melatonin.

3. Use according to claim 2, wherein said medicament includes at least one acrylic resin and is adapted for sustained release of melatonin.

4. Use according to claim 3, wherein said medicament is further adapted for regular release of said at least one compound.

5. Use according to any one of claims 1 to 4, wherein said at least one compound comprises a bicyclic fused ring system.

6. Use according to claim 5, wherein said bicyclic fused ring system includes at least two ring nitrogen atoms.

7. Use according to claim 6, wherein said bicyclic ring system comprises a pyrazolo[1,5-a]pyrimidine skeleton.

8. Use according to claim 7, wherein said at least one compound comprises zaleplon.

9. Use according to claim 6, wherein said bicyclic ring system comprises an imidazo[1,2,-a]pyridine skeleton.

10. Use according to claim 9, wherein said at least one hypnotic comprises zolpidem.

11. Use according to claim 6, wherein said bicyclic ring system comprises a pyrrolo[3,4-b]pyrazine skeleton.

12. Use according to claim 11, wherein said at least one hypnotic comprises zopiclone.

13. Use according to claim 6, wherein said bicyclic ring system comprises a triazolo[4,3-*a*]-pyridine skeleton.

14. Use according to claim 13, wherein said at least one hypnotic comprises trazodone.

15. A pharmaceutical formulation which comprises, in addition to at least one carrier, diluent, coating or adjuvant:

at least one compound selected from the group consisting of non-barbiturate and non-benzodiazepine hypnotics, and melatonin in an amount and form effective for short term potentiation of the hypnotic effect of said at least one compound.

16. A pharmaceutical formulation according to claim 15, which is further characterized by at least one of the following features:

(a) said hypnotics are GABA-A receptor modulators;

(b) said hypnotics are compounds which include a fused-ring system containing ring nitrogen;

(c) said formulation is in unit dosage form;